Marlboro
PM: MARL/01/03
MDSPS: AA05624

Informed Consent

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A RANDOMIZED, CONTROLLED STUDY OF THE SHORT-TERM EXPOSURE TO SMOKE CONSTITUENTS OF MARLBORO LIGHTS AND MARLBORO ULTRA LIGHTS COMPARED TO MARLBORO (FULL FLAVOR) CIGARETTES IN ADULT SMOKERS DURING CONTROLLED SMOKING

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MDSPS Project No: AA05624

Giving false, incomplete, or misleading information about your medical history, including past and present usage of medications, could have very serious consequences for your well being. It is vitally important that you provide a true and complete medical history.

Please read this form carefully and do not hesitate to ask the study physician any questions about this form and/or the information provided in it.

A. INTRODUCTION/PURPOSE

You are being asked to participate in a research study evaluating short-term exposure to the compounds that make up the smoke of cigarettes in adult smokers during confined smoking. This evaluation will be conducted by measuring identified biomarkers from cigarette smoke constituents in blood and urine. A biomarker is a biological substance or biological effect, which can be measured to evaluate a relationship between a foreign substance such as cigarette smoke and a body process.

This study is not intended to assess any medical treatment and, thus, alternative treatment is not appropriate. The only alternative to participating is not to participate. You will receive no medical benefit from your participation in this study. There are no costs to you for participating in the study. All study supplies and study procedures are provided to you at no cost.

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B. STUDY DESCRIPTION

Selected biomarkers in the blood and urine will be analyzed throughout the study. Initially, up to 140 healthy male and female adult volunteers who smoke Marlboro Full Flavor Kings, soft pack or hard pack, (hereinafter referred to as Marlboro) will be enrolled in the study.

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Source: https://www.industrydocuments.ucsf.edu/docs/ssdj0001

SCREENING VISIT:

Screening will take place within 28 days prior to the beginning of the study to determine eligibility for participation. Screening will include the following examinations:

- **Medical history** including the use of prescription and over-the-counter medications.
- **Physical examination,** which may include vital signs (blood pressure, temperature, heart rate, respiration rate), height, and weight.
- **Electrocardiogram** (ECG), which is a noninvasive evaluation of the electrical activity of the heart.
- **Pulmonary function testing** (PFT), which is a noninvasive assessment of the function of the lungs.
- **Blood** and **urine specimen collection** for general health screening to detect any abnormalities of the liver, kidneys, or immune system (such as infections and/or unknown health conditions) that may pose a risk to you, as well as a screening for HIV, hepatitis B, hepatitis C, the presence of drugs of abuse (Some drugs, particularly cannabis (marijuana), can be detected for several weeks.) and alcohol.
- **Pregnancy blood test** for all female study subjects.
- **Carboxyhemoglobin blood test** to verify that you are a smoker.
- **Smoking History Questionnaire** will be completed.
- **Fagerström Scale Questionnaire** to evaluate your smoking habits will be completed.

CLINIC CONFINEMENT/GROUP RANDOMIZATION:

You will receive a detailed time-and-events schedule. The study covers a study period of approximately 11 days. You will be confined to the clinic during the entire study period.

You may smoke approximately the same number of cigarettes per day during the entire study period that you reported as your normal cigarette consumption at screening. Randomization will occur on Day -1. All subjects will continue to smoke Marlboro prior to randomization.

You will check into the clinic on the evening of Day -3. At the time of check-in, a medical/medication history and a brief physical examination (including vital signs) will be conducted. In addition, a blood and urine sample will be collected for clinical laboratory tests, which will include a blood pregnancy test for females and urine screen for alcohol and drugs of abuse. A blood sample will also be drawn for a carboxyhemoglobin test to confirm that you are a smoker. You will also be required to complete a Diet, Consumption and Physical Activity Questionnaire. You will be required to give all of your cigarettes to the study staff. If you wish to smoke, you must ask the study staff, and you will be permitted to smoke Marlboro cigarettes until 11 PM that evening.

On the morning of Day -2, beginning at 7 AM, your cigarette consumption will be monitored in order to determine the number of cigarettes per day you will be permitted to smoke during the study. Your permitted maximum amount will be determined based on your normal cigarette consumption. Beginning on Day -2, smoking will only be permitted at designated times from 7 AM through 11 PM, and all cigarettes smoked will be documented by the study staff.

On the morning of Day -1, you will continue to smoke Marlboro at designated smoking times, divided over 3 periods throughout the day (see below), up to your daily allotment as determined from Day -2.

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Beginning on Day 1, 120 of the original 140 subjects will then be randomized (by chance, like flipping a coin) into 1 of the 3 groups. Those subjects that are not randomized to 1 of the 3 groups will be released from the study. There will be 40 subjects in each group. You will participate within your randomization group for the remainder of the study (Day 1 through the morning of Day 9). The 3 groups are as follow:

Group A	Marlboro
Group B	Marlboro LIGHTS
Group C	Marlboro ULTRA LIGHTS

You will be permitted to smoke Marlboro, Marlboro LIGHTS or Marlboro ULTRA LIGHTS cigarettes (depending on your group) up to your allotted number of cigarettes per day for the duration of the study. For all smoking groups, this allotment will be divided over 3 periods during the day (7AM to 12 noon, 12 noon to 5 PM, and 5 PM to 11 PM).

During the study, you will never be required to smoke ~~by the study staff~~. In addition, you may choose to quit smoking at any time. Subjects in the smoking groups who elect to quit smoking may do so and will continue in their assigned group and will finish the study according to that group's schedule. If you choose to smoke, you may smoke up to your daily allotment of cigarettes evenly divided over 3 periods throughout the day (see above) and a personal smoking schedule will be created based upon your daily cigarette allowance.

During the confinement period, a clinic menu will be served and will include meat and dairy products. No foods or beverages containing alcohol will be served. Consumption of caffeinated beverages will be permitted at specified meal times.

Engaging in strenuous exercise or activities during the confinement period will not be permitted.

On the morning of Day 8, or upon early termination, a physical examination, ECG, measurement of vital signs, measurement of weight, administration of questionnaires, and collection of blood and urine samples for clinical laboratory tests will be performed.

You will be released from the clinic following completion of the last 24-hour urine collection on the morning of Day 9.

Smoking Topography

Your puffing profile (topography) will be measured by a device designed to collect this information (CReSSmicro™ portable measurement device). On Days -2 through 8, you will be provided with the CReSSmicro™ portable measurement device and you will be required to use it while smoking your first cigarette of the day and the first cigarette after lunch.

Urine Collection

All urine voided will be collected throughout confinement beginning on the morning of Day -1 and ending on the morning of Day 9. You will be asked to void at specified times during the study to start and end collection intervals. In order to ensure that all urine is collected, the restroom doors will be locked throughout the collection period. A member of the clinic staff will provide you with a labeled collection container and will unlock the restroom door for you each time you need to enter the restroom.

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Vital Signs/Weight
Vital sign measurements and weight measurements will be performed at specified times throughout the study. Smoking will be prohibited for at least 15 minutes prior to each vital signs measurement.

Cigarette Butt Collection
All cigarette butts will be collected throughout the study.

Questionnaires
On Day –3, you will complete a Diet, Consumption, and Physical Activity Questionnaire. You will complete a Product Assessment Questionnaire and a Smoking Behavior Questionnaire daily on Days 1 through 8. On Day 8, you will complete a Fagerström Scale Questionnaire and an additional questionnaire to evaluate your smoking habits.

C. BLOOD COLLECTION

Blood samples will be collected for clinical laboratory tests at screening, check-in, and on Day 8 (including pregnancy testing for females) and for biomarker tests at Day -3 and on Days -1 through 8. It is anticipated that 21 venipunctures (insertion of needle into vein) will be required in this study, for a total of approximately 245 mL (8 ounces) of blood. If necessary for safety evaluations, additional samples may be collected.

D. POTENTIAL RISKS/ADVERSE EFFECTS OF STUDY PROCEDURES:

Potential adverse effects of pulmonary function tests include shortness of breath and dizziness.

The risks involved in drawing blood (venipuncture) include pain, discomfort, infection, bleeding and/or bruising at the puncture site, and fainting.

There is always the possibility that some unexpected adverse effect may develop in some persons participating in the procedures in this study. Trained medical personnel are available at MDS Pharma Services to provide immediate medical attention if required.

Cigarette smoking during pregnancy is associated with increased risk of spontaneous abortion, low birth weight infants, and prenatal mortality. Therefore, pregnant women cannot participate in this study, and women of childbearing potential must avoid becoming pregnant during the study. Nicotine passes freely into breast milk, and a nursing child may receive nicotine from a smoking mother's milk with the possibility of causing harmful side effects to the child. Therefore, women who are nursing cannot participate in this study.

Any significant or new findings that develop during the course of this study that may relate to your willingness to continue participation will be provided to you in writing in a timely manner.

E. REQUIREMENTS AND INSTRUCTIONS

Participation in this study requires that:

- You are generally healthy as determined by medical history, physical examination, ECG, pulmonary function testing, and clinical laboratory tests unless deemed not clinically significant by the study physician and/or study Sponsor.

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- You are an adult between 21 and 65 years of age (inclusive) and have a smoking history of manufactured non-menthol cigarettes of between 10 and 30 cigarettes per day for 12 months prior to study initiation.
- You have smoked Marlboro cigarettes (Kings, hard pack or soft pack) as your exclusive brand for a minimum of 4 weeks prior to study initiation.
- You have not used any other nicotine- or tobacco-containing product other than manufactured cigarettes (including roll-your-own cigarettes, bidis, snuff, nicotine inhaler, pipe, cigar, chewing tobacco, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum) within 4 weeks prior to study initiation.
- You are capable of understanding and are willing to sign this Informed Consent Form.

The study physician will review your medical/medication history, clinical laboratory results, ECG, pulmonary function tests, and physically examine you to determine your eligibility for this study. Following review of screening procedures by the study physician and/or study Sponsor, you will be declined entry into the study for the following reasons (the list is not all-inclusive):

- You have a clinically significant history or evidence (*i.e.*, findings from physical examination, vital signs, clinical laboratory tests, pulmonary function tests, ECG) of disease or abnormalities of any of the following body systems/body organs that, in the opinion of the study physician, would jeopardize your safety or impact the validity of the study results:
  - **Gastrointestinal** – related to the stomach/intestines, including conditions such as bleeding ulcers, inflammatory bowel disease, etc.
  - **Renal** – related to the kidneys, including conditions such as kidney stones, etc.
  - **Hepatic** – related to the liver, including conditions such as cirrhosis, hepatitis, jaundice, etc.
  - **Endocrine** – related to gland function, including conditions such as diabetes, thyroid disorders, etc.
  - **Oncologic** – related to cancers.
  - **Pulmonary** – related to the lungs/breathing, including conditions such as chronic obstructive pulmonary disease and tuberculosis, etc.
  - **Cardiovascular** – related to the heart and blood circulation system, including conditions such as heart attack, abnormal ECG, chest pain, congestive heart failure, etc.
  - **Neurological** – related to the brain and spinal cord, including conditions such as epilepsy, stroke, multiple sclerosis, seizures, etc.
  - **Psychiatric** – related to the brain in terms of behavior/emotions, including conditions such as depression, and addictions such as eating disorders, drug abuse, alcohol abuse, etc.
  - **Hematological** – related to the blood, including conditions such as anemia, clotting disorders, etc.
  - **Immunological** – related to the immune system, including conditions such as autoimmune diseases, AIDS, etc.
- You have any history (current or past) of congestive heart failure.
- You have an active fever of greater than 100.2°F at screening or at check-in.
- You have an acute (sudden-onset) illness (*e.g.*, upper respiratory infection, viral infection) requiring treatment with antibiotic medication within 2 weeks prior to study initiation.
- You have donated blood of 1 pint or more or received a whole blood or blood product transfusion within 56 days prior to study initiation.
- You have donated plasma within 7 days prior to study initiation.
- You have diabetes mellitus that cannot be controlled by diet and exercise alone (*i.e.*, requires treatment with prescription anti-diabetic medication or insulin therapy).

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- You require treatment with prescription or over-the-counter bronchodilator medications (*e.g.*, inhaled or oral β-agonists).
- You have a history of alcohol and/or drug abuse within the 12 months prior to study initiation.
- You have participated in a previous clinical study of an investigational drug, device, or biological product within 30 days prior to study initiation.
- You have a positive urine screen for alcohol and/or drugs of abuse at screening or at check-in.
- You or a first-degree relative (parent, sibling, child) are a current or former employee of the tobacco industry or a named party or class representative in litigation with Philip Morris USA.
- You or a first-degree relative are a current employee of MDS Pharma Services.
- If female, you are pregnant or nursing, or intend to become pregnant from screening through completion of the study.
- Your carboxyhemoglobin level at screening or check-in indicates that you are not a smoker.
- You are considered a puffer (a smoker who draws smoke from the cigarette into the mouth and throat, but does not inhale).

Restrictions For the Study

- Do not consume any foods or beverages containing alcohol during the 48 hours prior to the study. Alcohol will not be permitted during the study.
- Do not engage in strenuous exercise for 48 hours prior to the study. Strenuous exercise will not be permitted during the study.
- If you are a woman of childbearing potential (i.e., not surgically sterile by hysterectomy or tubal ligation at least 6 months prior to study initiation or at least 2 years naturally postmenopausal) and sexually active, you must agree to use one of the following methods of birth control:
    - hormonal (*i.e.*, oral, transdermal patch, implant, or injection) consistently for at least 3 months prior to Day –1,
    - double barrier (*i.e.*, condom with spermicide or diaphragm with spermicide) consistently for at least 2 weeks prior to Day –1,
    - IUD for at least 2 weeks prior to screening, or
    - have a partner who has been vasectomized for at least 6 months prior to Day -1.

Females must also accept the risk that pregnancy might result even while using these methods of birth control.

F. CONFIDENTIALITY

Information collected during the study will be considered confidential and will be retained in a secure database by MDS Pharma Services and the study Sponsor. All of this confidential information is subject to review by the appropriate staff and representatives on behalf of the Sponsor, the Institutional Review Board, and possibly regulatory authorities, for verification of clinical procedures and/or data. Your permission for such review of your confidential information is granted by signing this document. For purposes of study reporting, you will be identified by initials and numbers only. However, your name, address, telephone number, and an individual to contact in case of an emergency will be kept in the record of the study physician at MDS Pharma Services in case you need to be contacted in the future about this study. Where required by law or statute, some medical results will be reported to health authorities. The results of this study may be published but will not disclose your identity.

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G. ACKNOWLEDGMENT

I understand that:

- At the conclusion of the study, regardless of whether I have chosen to smoke or quit smoking during the study, MDS Pharma Services will pay me up to $2,700.00 by check for my participation in this study. If I am not randomized to one of the 3 study groups, MDS Pharma Services will pay me up to $700.00 for my participation in this study. If for any reason I do not complete the study (*i.e.*, I am dropped by the study physician and/or Sponsor, I am dropped for not following the directions/instructions of the study staff, I choose to discontinue, or the study is discontinued by the study physician and/or Sponsor), I will be paid on a prorated basis. No deductions for any state or federal withholding or any other similar taxes will be made. I am solely responsible for reporting such payment on my state and federal tax returns and for the payment of any taxes due for the receipt of these payments from MDS Pharma Services.
- To reduce the health effects of smoking, the best thing to do is to quit smoking.
- Participating in this study does not make me an employee of the Sponsor or MDS Pharma Services.
- While involved in this study, I will have direct access to medical attention.
- It may be unsafe for me to leave the clinic during the study before being examined by MDS Pharma Services medical personnel.
- If I become physically injured or ill as a direct result of participation in this research study, MDS Pharma Services will provide the medical treatment necessary to assist in my recovery from the injury or illness. There will be no charge to me for this care beyond what is covered by my health insurance. This agreement to provide free medical treatment does not include treatment for any illness or injury I might experience during the course of the study if the illness or injury is not the result of the research study. No compensation other than free medical treatment of the injury or illness will be provided.
- Provision of medical treatment shall not be an admission by MDS Pharma Services, or the Sponsor that my injury or illness is study related.
- If I experience an adverse reaction or injury while participating in this research study, I will contact MDS Pharma Services' 24-hour Nurse's Line by calling (402) 790-4742. If I wish to contact the physician in charge of this study, I will call Dr. James C. Kisicki at (402) 476-2811 or, if after 4:30 p.m. or on weekends, at (402) 610-0111. Since the physician may not always be immediately available, the 24-hour Nurse's Line should be utilized.

H. CONSENT

I have read this written informed consent document and freely consent to participate in this study.

I understand:

- The nature of the study.
- I am a voluntary subject.
- The physician in charge can remove me from the study without my consent, either because of my failure to follow the study requirements or if the physician feels it is medically in my best interest.
- The study includes examinations, including blood examinations, to which I will be subjected.
- The Sponsor may stop the study, or discontinue my participation, at any time at its discretion.
- Procedures in this study may be associated with undesirable effects, some of which may not be known.
- I may choose to withdraw from the study at any time.

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- I may refuse to participate or withdraw from participation at any time without penalty or loss of benefits to which I am otherwise entitled (I may be paid for my participation on a prorated basis.).
- Nothing contained in this informed consent waives any of my legal rights as a volunteer, nor does it release the study physician, the Sponsor, MDS Pharma Services or its agents from any liability for negligence.

I agree to adhere to the regulations and directions of the study as outlined. I have been told how long and by what methods the study will be carried out, and I have been reminded that I have the opportunity to ask further questions about the details and procedures of the study.

All my questions have been satisfactorily answered. I have received a signed and dated copy of this consent form.

If I have any further questions regarding my rights as a volunteer, I will contact Frank E. Landis Jr., J.D., of the MDS Pharma Services Institutional Review Board at **1-800-776-1716.**

If I have any further questions about the study, I will contact MDS Pharma Services' 24-hour Nurse's Line by calling **(402) 790-4742**.

I. CERTIFICATION

I certify that I am between 21 and 65 years of age (inclusive) and have no known existing undisclosed medical problems.

I certify that I understand and meet the requirements for study participation as outlined in Section E (Requirements and Instructions), and will adhere to instructions of the study staff during the course of the study.

My signature below certifies that I understand the research investigation discussed above.

If female, I certify that I am not pregnant and not nursing.

Witness my signature this _____ day of _____ 20 __

Print Name: _____ Signature: _____

Person Administering Informed Consent: _____ _____
(Print) (Signature)

Date: _____ Time:_____ MDS Pharma Services ID No.: _____

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